Short Title

CSR for Protocol C-09-055

Long Title

Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% for Prevention and Treatment of Ocular Inflammation and Pain after Cataract Surgery

1. TITLE PAGE

Operations Unit Number/Name:	96/Clinical Trial Management			
Project Name/Number:	Nepafenac/225021			
Name of Test Article/ Investigational Product:	Nepafenac Ophthalmic Suspension, 0.3%			
Indication Studied/Supported:	Ocular pain and inflammation associated with cataract surgery			
Study Description:	Double-masked, parallel-group, multicenter, vehicle-and active-controlled, randomized study			
Name of Sponsor:	Alcon Research, Ltd.			
Development Phase of Study:	Phase 3			
Study Initiation Date:	23 June 2010			
Date of Early Termination:	Not applicable			
Study Completion Date:	25 May 2011			
Name and Affiliation of Principal or Coordinating Investigator(s):	Robert Lehmann, MD Lehmann Eye Center Nacogdoches, TX			
Name of Sponsor's Responsible Medical Officer:	Stephen Lane, MD Associated Eye Physicians & Surgeons, Ltd. Shoreview, MN			
Name of Company/Sponsor Signatory:	Michael J. Brubaker, PhD, Vice President External Disease Development			
Report Status:		Interim		Abbreviated
	X	Final	X	Full
Approvals:	See last page for electronic approvals.			

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), including the archiving of essential documents. The approval signature of 'Clinical Management' on this report signifies that quality control processes were complete, including verification the report fully and accurately describes all test methods, data, discussions, and conclusions resulting from the study/research.

1.1. Comprehensive Cumulative History

Not applicable.

2. SYNOPSIS

Name of Sponsor/Company: Alcon Research, Ltd.	
Name of Finished Product: Nepafenac Ophthalmic Suspension, 0.3%	
Name of Active Ingredient: Nepafenac 0.3% (AL-6515)	
Title of Study: Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% for Prevention and Treatment of Ocular Inflammation and Pain after Cataract Surgery	
Investigator(s) and Study Center(s): For details see Section 16.1.4. A total of 65 sites randomized patients; 49 in the United States, 6 in Hungary, 4 in Italy, 4 in Sweden, and 2 in Switzerland.	
Publication(s): None	
Study Period: 23 June 2010 – 25 May 2011	Phase of Development: Phase 3

Objectives:

Primary efficacy:

- Nepafenac Ophthalmic Suspension, 0.3% (Nepafenac 0.3%) dosed once daily is noninferior to Nepafenac Ophthalmic Suspension, 0.1% (NEVANAC) dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to Nepafenac Ophthalmic Suspension, 0.3% Vehicle (Nepafenac Vehicle 0.3%) dosed once daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- NEVANAC dosed 3 times daily is superior to NEVANAC Vehicle dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

Secondary efficacy:

- Nepafenac 0.3% dose once daily is noninferior to NEVANAC dosed 3 times daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to Nepafenac Vehicle 0.3% dosed once daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.
- NEVANAC dosed 3 times daily is superior to NEVANAC Vehicle dosed 3 times daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.

Supportive efficacy objectives:

- To further characterize the efficacy of Nepafenac 0.3% relative to the comparator groups at days 1, 3, and 7 for the primary and secondary endpoints, and at all on-therapy visits for assessment of treatment failures.

Name of Sponsor/Company: Alcon Research, Ltd.
Name of Finished Product: Nepafenac Ophthalmic Suspension, 0.3%
Name of Active Ingredient: Nepafenac 0.3% (AL-6515)
Safety objectives: • To demonstrate that topical ocular use of Nepafenac 0.3% dosed once daily for up to 14 days after cataract extraction is safe and well tolerated, and consistent with the established safety profile of NEVANAC.
Methodology: Double-masked, parallel-group, multicenter, vehicle-and active-controlled, randomized study
Number of Patients Planned/Analyzed: 2000 patients planned / 2042 analyzed
Diagnosis and Main Criteria for Inclusion: Adult patients of any race and either sex, requiring cataract extraction by phacoemulsification with planned implantation of a posterior chamber intraocular lens
Test Product, Dose and Mode of Administration, Batch Number(s): Test Product: Nepafenac Ophthalmic Suspension, 0.3% (*Referred to as Nepafenac 0.3%)* Dose: 1 drop, once daily. An additional dose was administered between 30-120 minutes prior to surgery. Mode of Administration: Batch Number: 10-501170-1; FID 115535
Duration of Treatment: 16 days (1 day prior to surgery, continuing on the day of surgery, and for 14 days following surgery)
Reference Therapy, Dose and Mode of Administration, Batch Number(s): Reference Product: Nepafenac Ophthalmic Suspension 0.3% Vehicle (*Referred to as Nepafenac Vehicle 0.3%*) Dose: 1 drop, once daily. An additional dose was administered between 30-120 minutes prior to surgery. Mode of Administration: topical ocular Batch Number: 10-501165-1; FID 115856 Reference Product: Nepafenac Ophthalmic Suspension, 0.1% (*Referred to as NEVANAC*) Dose: 3 times daily Mode of Administration: topical ocular Batch Number: 10-501158-1; FID 105022 Reference Product: NEVANAC Vehicle (*Referred to as NEVANAC Vehicle)* Dose: 3 times daily Mode of Administration: topical ocular Batch Number: 10-501153-1; FID 104285

Name of Sponsor/Company: Alcon Research, Ltd.
Name of Finished Product: Nepafenac Ophthalmic Suspension, 0.3%
Name of Active Ingredient: Nepafenac 0.3% (AL-6515)
Criteria for Evaluation: Primary Efficacy: • The proportion of patients with a cure at Day 14. Cure was defined as a score of 0 for both aqueous cells and flare. Secondary Efficacy: • The proportion of patients who were pain-free as assessed by the Investigator at Day 14. Pain-free was defined as a score of 0 on the Investigator rating scale which ranged from 0 (none) to 5 (severe). Supportive Efficacy: • The proportion of patients with a cure at Days 1, 3, and 7 (and remaining a cure at all subsequent visits). • The proportion of patients who were pain-free as assessed by the Investigator at Days 1, 3, and 7 (and remained pain-free at all subsequent visits). • The proportion of patients who were declared a treatment failure. Patients who had an aqueous cells score of ≥ 3, aqueous flare score = 3, and/or an ocular pain score ≥ 4 were defined as a treatment failure. Exploratory Analysis of Primary Variable: • The proportion of patients that were a clinical success which was defined as cells score ≤ 1 (0-5 cells) and flare score = 0 Safety: • Adverse events, best-corrected visual acuity, intraocular pressure (IOP), slit-lamp parameters (corneal edema, bulbar conjunctival injection, chemosis), dilated fundus parameters (retina/macula/choroid, optic nerve)

Name of Sponsor/Company: Alcon Research, Ltd.
Name of Finished Product: Nepafenac Ophthalmic Suspension, 0.3%
Name of Active Ingredient: Nepafenac 0.3% (AL-6515)
Statistical Methods: For comparison of the 2 nepafenac groups, a 2-tailed 95% confidence interval was calculated for the difference (Nepafenac 0.3% - NEVANAC) in cure rates at Day 14. Stratification was by Investigator to match the stratification used in the randomization process. The noninferiority margin was 10 percentage points, meaning that the lower limit of the 2-sided 95% confidence interval must have been greater than -10% to establish noninferiority. For comparison of active versus vehicle treatment groups, the proportion of patients who were cured was compared between pairs of treatment groups (NEVANAC versus NEVANAC Vehicle; Nepafenac 0.3% versus Nepafenac Vehicle 0.3%) using the Cochran-Mantel-Haenszel test. Each test was reported at the 5% significance level, 2-sided. Stratification for Investigator was used in the Cochran-Mantel-Haenszel test to match stratification used in the randomization process. The comparisons of active to vehicle were reported using only the vehicle group with the same dosing frequency. Analysis of the Investigator's assessment of ocular pain, was analogous to the analyses described above for the primary endpoint. Comparisons of the active groups with the vehicle groups were reported using only the vehicle group with the same dosing to assess assay sensitivity and the efficacy of the investigational product. The analysis of the supportive efficacy variables was descriptive only. The proportion of patients with clinical cures at each visit, the proportion of patients who were pain-free at each visit, and the proportion of patients who were declared a treatment failure were calculated for each treatment group.

Efficacy Results:

Primary inferences were based upon the intent-to-treat data set. A total of 2022 patients received study medication and had at least 1 scheduled on-therapy visit and were included in the intent-to-treat analysis. The primary efficacy variable in this study was a binary outcome of cure for inflammation which required a score of 0 for both cells (0 cells present) and flare (no flare present).

The lower bound of the 95% 2-sided confidence interval (-5.73%, 3.17%) is greater than -10%; therefore, the primary noninferiority efficacy results show Nepafenac 0.3% dosed once daily is noninferior to NEVANAC dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction (Table 2.-1).

Table 2.-1:
Percent Patients Cured at Day 14
Active Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC			
N	n (%)	N	n (%)	95% CI*	p-value
807	552 (68.4)	811	568 (70.0)	(-5.73, 3.17)	< 0.0001

Cure was defined as a patient having a score of 0 for both cells and flare at Day 14, last observation carried forward (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
*Test based confidence interval for difference of treatment proportions (Nepafenac 0.3% - NEVANAC) using the method of Yanagawa, Tango and Hiejima.
If the lower bound of the confidence interval (CI) for (Nepafenac 0.3% - NEVANAC) is greater than the noninferiority margin -10%, then the data support the noninferiority of Nepafenac 0.3% versus NEVANAC .
p-value is based upon the method of Yanagawa, Tango and Hiejima for demonstrating noninferiority.
p-values less than 0.025 indicate that the data support the noninferiority of Nepafenac 0.3% versus NEVANAC.

Primary superiority efficacy results show that Nepafenac 0.3% is superior to Nepafenac Vehicle 0.3% ($p < 0.0001$), and NEVANAC is superior to NEVANAC Vehicle ($p < 0.0001$), for the prevention and treatment of ocular inflammation 14 days after cataract extraction (Table 2.-2).

Table 2.-2
Percent Patients Cured at Day 14
All Treatments Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	552 (68.4)	811	568 (70.0)	197	67 (34.0)	205	73 (35.6)	< 0.0001	< 0.0001

Cure was defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
p-value is based upon Cochran-Mantel-Haenszel controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

The secondary efficacy variable was the percent of patients with no ocular pain as assessed by the Investigator on a 5-point ordinal scale. A score of 0 indicated no ocular pain. The lower bound of the 95% 2-sided confidence interval (-3.08%, 2.70%) is greater than -10%; therefore, the secondary noninferiority efficacy results show that Nepafenac 0.3% is noninferior to NEVANAC for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction (Table 2.-3).

Table 2.-3:
Percent Pain-Free Patients at Day 14
Active Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC			
N	**n (%)**	**N**	**n (%)**	**95% CI***	**p-value**
807	734 (91.0)	811	737 (90.9)	(-3.08, 2.70)	<0.0001

Pain-free was defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
*Test based confidence interval for difference of treatment proportions (Nepafenac 0.3% - NEVANAC) using the method of Yanagawa, Tango and Hiejima.
If the lower bound of the confidence interval (CI) for (Nepafenac 0.3% - NEVANAC) is greater than the noninferiority margin -10%, then the data support the noninferiority of Nepafenac 0.3% versus NEVANAC.
p-value is based upon the method of Yanagawa, Tango and Hiejima for demonstrating noninferiority.
p-values less than 0.025 indicate that the data support the noninferiority of Nepafenac 0.3% versus NEVANAC.

Secondary superiority efficacy results show that Nepafenac 0.3% and NEVANAC are superior to their respective vehicles for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction, ($p < 0.0001$) (see Table 2.-4).

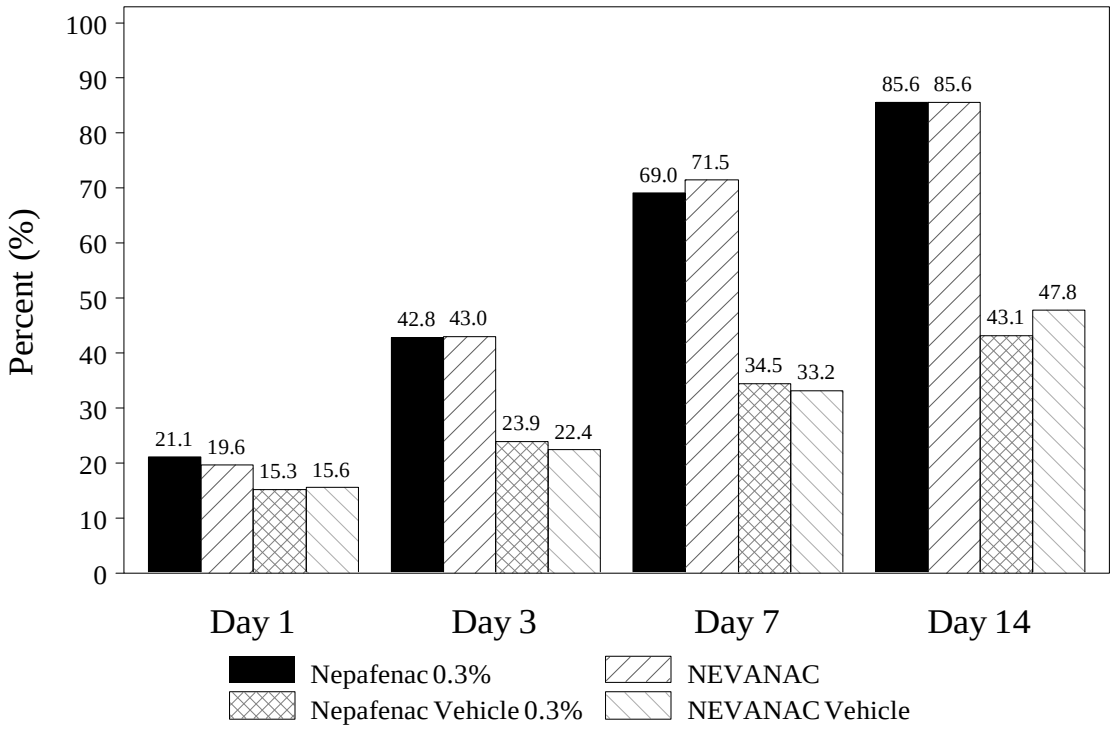
Table 2.-4:
Percent Pain-Free Patients at Day 14
All Treatments Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	734 (91.0)	811	737 (90.9)	197	98 (49.7)	205	115 (56.1)	< 0.0001	< 0.0001

Pain-free was defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
p-value is based upon Cochran-Mantel-Haenszel controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

Although the primary endpoint was based upon cures (cells score + flare score = 0) which is absence of inflammation, clinical success is also believed to be a clinically relevant indicator of inflammation resolution. Clinical success allows trace inflammation and is defined as cell score ≤ 1 (0-5 cells) and a flare score = 0. Results of an additional unplanned assessment for cumulative clinical success demonstrate Nepafenac 0.3% is superior to Nepafenac Vehicle 0.3% at all postoperative visits including Day 1 ($p = 0.0264$ Day 1, $p < 0.0001$ Days 3-14). This same difference was not observed in the NEVANAC group compared with the NEVANAC Vehicle group until Day 3 ($p < 0.0001$) (see Figure 2-1 on the following page).

Figure 2-1
Percent Cumulative Clinical Success by Visit
(Intent-to-Treat)



Safety Results:

The safety evaluation was conducted on all patients who were exposed to the study drug. The safety analysis was based upon an evaluation of the following: adverse events, best-corrected visual acuity, IOP, slit-lamp parameters (corneal edema, bulbar conjunctival injection, chemosis), and dilated fundus parameters (retina/macula/choroid, optic nerve).

Treatment-emergent adverse events are summarized in Table 2.-5.

Treatment-emergent adverse events were reported in 253 patients. Of these, there were 3 adverse reaction events that were assessed by the study Investigator to have a causal relationship to study drug. No deaths occurred in patients receiving any test article during the study. There were 10 serious adverse events: 7 in the Nepafenac 0.3% group and 3 in the NEVANAC group. A total of 47 patients withdrew because of an adverse event.

Table 2.-5:
Summary of Treatment-Emergent Adverse Events

	Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle	
	N = 817		N = 819		N = 201		N = 205	
Adverse Event Category	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Deaths	0	0.0	0	0.0	0	0.0	0	0.0
Patients experiencing nonfatal serious adverse events[a]	7	0.9	3	0.4	0	0.0	0	0.0
Patients discontinued due to an adverse event	15	1.8	17	2.1	9	4.5	6	2.9
Discontinued due to nonfatal serious adverse events	2	0.2	2	0.2	0	0.0	0	0.0
Discontinued due to nonserious adverse events	13	1.6	15	1.8	9	4.5	6	2.9
Treatment-related	1	0.1	0	0.0	0	0.0	0	0.0
Not related to treatment	12	1.5	15	1.8	9	4.5	6	2.9
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	99	12.1	82	10.0	39	19.4	33	16.1
Most frequent treatment-emergent adverse events (incidence of 1% or greater in active treatment groups)								
Headache	22	2.7	13	1.6	3	1.5	3	1.5
Intraocular pressure increased	8	1.0	7	0.9	0	0.0	0	0.0
Patients with at least 1 treatment-emergent adverse related to treatment (ADR; adverse drug reaction)								
Eye pain	1	0.1	0	0.0	0	0.0	1	0.5
Hypersensitivity	1	0.1	0	0.0	0	0.0	0	0.0

[a]All nonfatal serious adverse events were assessed as unrelated to the use of study medication

The most common treatment-emergent ocular adverse events (ie, those occurring at rates ≥ 1.0%) are provided in Table 14.3.1.5.-1. Increased IOP was the most common treatment-emergent adverse event reported. Increased IOP is a common occurrence after cataract surgery and the incidences of increased IOP were essentially the same in the Nepafenac 0.3% and NEVANAC treatment groups.

Table 14.3.1.5.-1:
Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0%

	Nepafenac 0.3% N=817		NEVENAC N=819		Nepafenac Vehicle 0.3% N=201		NEVANAC Vehicle N=205	
Coded Adverse Event	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Eye disorders								
Eye pain	2	0.2	1	0.1	3	1.5	7	3.4
Posterior capsule rupture	5	0.6	4	0.5			2	1.0
Photophobia					5	2.5	5	2.4
Corneal oedema	2	0.2			4	2.0	2	1.0
Iritis			4	0.5	3	1.5	1	0.5
Eye irritation	2	0.2	2	0.2	2	1.0	1	0.5
Eye inflammation	1	0.1			2	1.0	2	1.0
Visual acuity reduced					3	1.5	1	0.5
Ocular hyperaemia							3	1.5
Vision blurred							2	1.0
Injury, poisoning and procedural complications								
Injury	5	0.6	1	0.1	2	1.0	1	0.5
Cataract operation complication			4	0.5	3	1.5		
Investigations								
Intraocular pressure increased	8	1.0	7	0.9				
Nervous system disorders								
Headache	22	2.7	13	1.6	3	1.5	3	1.5

Coded adverse event = MedDRA Preferred Term (version 13.0) presented by System Organ Class.

The most common treatment-emergent nonocular adverse event was headache. Headache was reported as a common adverse event in previous clinical studies and therefore was not unexpected in this study. Although there was a higher incidence of AEs for headache in the Nepafenac 0.3% group, the incidence of headaches requiring treatment was similar across all treatment groups: Nepafenac 0.3% = 84 (10.3%), NEVANAC = 84 (10.3%), Nepafenac Vehicle 0.3% = 14 (7.0%), and NEVANAC Vehicle = 17 (8.3%).

There were 3 cases of adverse reactions accessed as related to study medication. Two of these involved eye pain, 1 in the Nepafenac 0.3% treatment group (0.1%), and 1 in the NEVANAC Vehicle treatment group (0.5%). The third adverse reaction was hypersensitivity, which was reported in the Nepafenac 0.3% treatment group (0.1%). None of these adverse reactions met the definition of a serious adverse event; all were mild to moderate in intensity, and all resolved with or without treatment. The patient experiencing hypersensitivity discontinued as a result of the adverse reaction.

In general, no safety issues or trends were identified based upon changes from baseline in best-corrected visual acuity, IOP, slit-lamp parameters (corneal edema, bulbar conjunctival injection, chemosis), or dilated fundus parameters (retina/macula/choroid, optic nerve).

Overall Conclusion:

- **Nepafenac 0.3% given once a day is as effective as NEVANAC given 3 times a day for prevention and treatment of pain and inflammation following cataract surgery. The safety of Nepafenac 0.3% is comparable to Nevanac with the added benefit of reduced treatment burden and improved convenience.**

Efficacy Results:

- **Nepafenac 0.3% and NEVANAC are superior to their respective Vehicles for the prevention and treatment of ocular pain and inflammation.**
    - **Nepafenac 0.3% is superior to its Vehicle based on cumulative percentage of patients who were cures beginning at Day 7 postoperatively ($p < 0.0001$)**
    - **Nepafenac 0.3% is superior to its Vehicle based on the cumulative percentage of patients who were pain-free at each postoperative visit ($p < 0.0001$)**
    - **Nepafenac 0.3% is superior to its Vehicle based on cumulative percentage of patients who were clinical successes at each postoperative visit (Day 1, $p=0.0264$, Days 3, 7, 14, $p < 0.0001$)**
    - **NEVANAC is superior to its Vehicle based on cumulative percentage of patients who were cures beginning at Day 7 postoperatively ($p < 0.0001$)**
    - **NEVANAC is superior to its Vehicle based on the cumulative percentage of patients who were pain-free at each postoperative visit ($p < 0.0001$)**
    - **NEVANAC is superior to its Vehicle based on cumulative percentage of patients who were clinical successes beginning at Day 3 postoperatively ($p < 0.0001$)**
    - **Nepafenac 0.3% dosed once daily is comparable to NEVANAC dosed 3 times daily**

for the prevention and treatment of ocular pain and inflammation.

- **Nepafenac 0.3% was noninferior to NEVANAC based on the percentage of cures at Day 14 postoperatively (lower bound of 95% 2-sided confidence interval for the difference between treatments of -5.73%).**

- **Nepafenac 0.3% was noninferior to NEVANAC based on the percentage of patients who were pain-free at Day 14 postoperatively (lower bound of 95% 2-sided confidence interval for the difference between treatments of -3.08%).**

Efficacy Conclusion:

- **Nepafenac 0.3% given once daily was equally effective as NEVANAC given 3 times daily for the prevention and treatment of pain and inflammation following cataract surgery.**

Safety Results:

- **A review of adverse events, both treatment-related and treatment-emergent, revealed no individual events that would represent a previously unknown safety issue or impact the overall favorable risk benefit profile of Nepafenac.**

- **A review of measured safety parameters, including changes from baseline in best-corrected visual acuity, intraocular pressure, slit-lamp examination, and fundus examination, revealed similar findings between treatment groups with observed changes being within expected limits for postoperative cataract patients.**

Safety Conclusion:

- **Based upon a review of adverse events and ocular safety parameters, no safety concerns were identified for Nepafenac 0.3% after dosing for 14 days following cataract surgery in a population of adult and elderly patients. The safety profile of Nepafenac 0.3% is comparable with the safety profile of NEVANAC**

Study Number

C-09-055

Substantial Protocol Amendments

Amendment 1

Purpose of Amendment: The purpose of Amendment 1 is to increase the estimated sample size, revise inclusion criteria and several exclusion criteria as well as clarify language about the test article and its storage. In addition, editorial changes were made to improve clarity. The revisions along with the rationale are described below.

Revision 1:

The sample size justification section is modified to reflect an increase in estimated sample size to 2000 patients and delete the reference to the number of per protocol evaluable patients.

Rationale: The increase in estimated sample size is required to attain adequate power for rejecting all three null hypotheses (i.e. non-inferiority of Nepafenac Ophthalmic Suspension, 0.3% to NEVANAC, superiority of Nepafenac Ophthalmic Suspension, 0.3% to vehicle and superiority of NEVANAC to vehicle) in case there is a small numerical difference between active treatments.

Revision 2:

An inclusion criterion is added indicating that the study eye of patients enrolled will be expected, in the opinion of the investigator, to experience a functional improvement in best corrected visual acuity (BCVA) after surgery.

Rationale:

This change will be implemented as an acknowledgment of sound medical practice.

Revision 3:

An inclusion criterion is modified to clarify that a legally authorized representative of the patient can provide informed consent.

Rationale:

This change is implemented to be consistent with section 9.1.1 of the protocol.

Revision 4:

Exclusion criteria are added to specify that patients with planned multiple procedures (eg. trabeculectomy, corneal transplant) during cataract surgery, patients with lens pseudoexfoliation syndrome and those diagnosed as uncontrolled glaucoma will not beenrolled.

Rationale:

Patients who require multiple surgical procedures will likely develop more inflammation postoperatively and need additional therapy. Patients with lens pseudoexfoliation syndrome where glaucoma or zonular compromise is present are at increased risk of surgical complications. Patients with uncontrolled glaucoma are at increased risk of postoperative complications. Consequently, the above exclusion criteria were added to ensure safety and to avoid confounding the study results.

Revision 5:
The proliferative diabetic retinopathy exclusion criterion is expanded to exclude patients who in the opinion of the investigator are at increased risk of developing postoperative macular edema (e.g. diabetic retinopathy).
Rationale:
Since a portion of the patients will receive only vehicle for 14 days after surgery, any patient that is thought to be at increased risk of developing postoperative macular edema should be excluded for patient safety.

Revision 6:
The criterion that excludes patients with an investigational intraocular lens is expanded to clarify that patients should not be participating in any other investigational drug/device study within 30 days before cataract surgery.
Rationale:
In keeping with good clinical practice patients should not be enrolled in two clinical studies at the same time. This modification will help ensure that sites follow best practice.

Revision 7:
The test article information is revised to indicate the products should be stored according to the label.
Rationale:
This change was performed to ensure proper storage of test articles at the sites.

Revision 8:
The test article labeling language is changed from randomization number to kit number and also patient number is changed to subject number in the randomization sequence description.
Rationale:
The terms kit number and subject number are added to be consistent with the randomization terminology used in the IVR system.

Revision 9:
Section 6.2 is modified to include details about the dosing card which will be included in the kit.
Rationale:
This section is modified to ensure that sites understand the details regarding the test article kit and its corresponding instructions.

Revision 10:
Section 9.2 is modified to clarify the procedure for patients that exit the study prior to a postoperative visit.
Rationale:
The change was implemented to clarify the procedure.

Study Number: C-09-055

Investigator Sites

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11	Alcon Investigational Site Albany, GA 317xx, USA
12	Eye Care Centers Management Inc. Clayton Eye Center 1000 Corporate Center Drive, Morrow, GA 30260, USA
13	The Eye Center of North Florida 2500 Martin Luther King Jr. Blvd. Panama City, FL 32405, USA
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17	Alcon Investigational Site Bloomfield Hills, MI 483xx; USA
18	Alcon Investigational Site Parker, CO 801xx, USA
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24	Alcon Investigational Site Chicago, IL 606xx, USA
25	Alcon Investigational Site Nacogdoches, TX 759xx, USA
26	Alcon Investigational Site Tamarac, FL 333xx, USA
27	Physicians Independent Medical Group Arch Health Partners 15611 Pomerado Road, Poway, CA 92064, USA
28	Department of Ophthalmology Norrlands University Hospital, SE-901 85, Umea, Sweden
29	Ophthalmology Associates 12990 Manchester Road, St. Louis, MO 6313, USA
30	Ohio State University Dept. of Ophthalmology 915 Olentangy River Road, Columbus OH 43212, USA
31	California Eye Institute 1360 Herndon, Fresno, CA 93720, USA
32	Alcon Investigational Site Poughkeepsie, NY 126xx, USA

33	U.O. Oculistica Universitaria A.O.U.P. Nuovo Ospedale S. Chiara Presidio Ospedaliero di Cisanello Edificio 30 Via Paradisa 2 Pisa-Cisanello, 56124, Italy
34	Alcon Investigational Site Fort Worth, TX 761xx, USA
35	Vaszary Kolos Hospital Ear-Nose and Throat-Ophthalmology Petőfi Sandor u. 26-28 H-2500 Esztergom, Hungary
36	Mid Florida Eye Center, PA 17560 West US Highway 441 Mt. Dora, FL 32757, USA
37	Semmelweis University Tömő u. 25-29 H-1083, Budapest, Hungary
38	Danbury Eye Physicians & Surgeons PC 69 Sand Pit Road, Danbury, CT 06810, USA
39	Eye Care Assoc. of East Texas 2440 E. Fifth Street Tyler, TX 75701, USA
40	Alcon Investigational Site Phoenix, AZ 850xx, USA
41	Valihallas Eyeclinic AB Odengatan 1 SE-114 24, Stockholm, Sweden
42	Ophthalmic Consultants of Boston 50 Staniford Street, Boston, MA 02114, USA
43	Clinica Oculistica, Fondazione IRCCS Cá Granda - Ospedale Maggiore Policlinico Via Manfredo Fanti, 6 20122-Milano, Italy
44	North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Mission Hills, CA 91345, USA
45	Alcon Investigational Site Kingston, PA 18xxx, USA
46	Alcon Investigational Site San Antonio, TX 782xx, USA

47	Eastside Westside Research Center 1413 John B. White, Sr. Blvd., Spartanburg, SC 29306, USA
48	Alcon Investigational Site Artesia, CA 907xx, USA
49	Clinical Research Center of Wheaton Eye Clinic, LLC 2015 N. Main Street Wheaton, IL 60187, USA
50	Alcon Investigational Site Norfolk, VA 235xx, USA
51	Alcon Investigational Site Miami, FL 331xx, USA
52	Alcon Investigational Site Bel Air, MD 210xx, USA
53	Hôpital Ophtalmique Jules-Gonin Université de Lausanne Av. de France 15 1004 Lausanne, Switzerland
54	Alcon Investigational Site San Antonio, TX 782xx, USA
55	Alcon Investigational Site Kansas City, MO 641xx, USA
56	Alcon Investigational Site Fort Myers, FL 339xx, USA
57	Kenézy Hospital Bartók Béla út 2-26 H-4043, Debrecen, Hungary
58	Cornerstone Eye Care 307 N. Lindsay Street Highpoint, NC 27262, USA
59	Alcon Investigational Site Sioux Falls, SD 571xx, USA
60	Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756, USA
61	Azienda Opedaliero Univesitaria San Martino V.le Benedetto XV, 5 Genova, 16132, Italy
62	Jósa András Hospital Ophthalmology Department Szent István str. 68 11-4400, Nyíregyháza, Hungary

63	Boozman-Hof Regional Clinic, PA 3737 West Walnut Street Rogers, AR 72756, USA
64	Texan Eye, PA 5717 Balcones Drive Austin, TX 78731, USA
65	Vistar Eye Center 375 Hernbarger Rd. Roanoak, VA 24012, USA

Datum des Berichts

06. Oktober 2017